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ARMY DRUG DEVELOPMENT PROGRAM PHASE I CLINICAL TESTING

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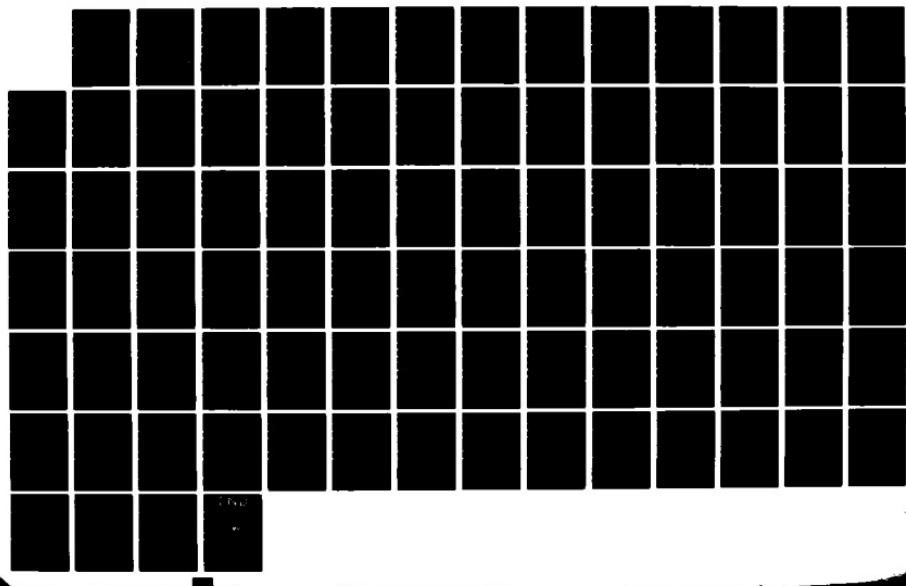
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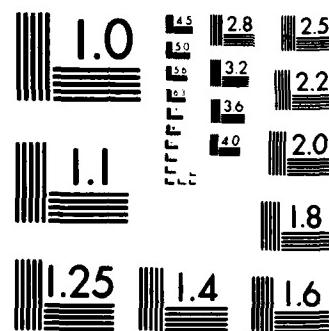
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Army Drug Development Program
Phase I
Clinical Testing

Annual Report
February 1981-January 1982

Richard Reba, M.D.

February 1982

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-75-C-5036

BIO-MED, Inc.
4401 Hartwick Road
College Park, Maryland 20740

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) From February 1981 through January 1982, research was continued at BIO-MED, Inc. under contract DAMD17-75-C-5036 "Phase I Clinical Studies: The Army Drug Development Program". Activities under this contract include : Experiment #17: WR 180,409 H ₃ PO ₄ : Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics. Experiment #18: WR 194,965 H ₃ PO ₄ : Safety and Tolerance to Three Divided Doses, Rising Dose Levels.		

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Army Drug Development Program
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SUMMARY

In this reporting period, BIO-MED, Inc. continued to design and implement Phase I clinical studies in support of the Army's drug development program.

A study of WR 180,409 H₃PO₄, a pyridinemethanol with demonstrated activity against chloroquine resistant falciparum malaria, was completed. In previous Phase I clinical studies conducted by BIO-MED, Inc., gastrointestinal intolerance to a single oral 750 mg dose of WR 180,409 H₃PO₄ was observed. As a result, the multiple dose study reported here (Experiment #17, WR 180,409 H₃PO₄: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics) was implemented. In a double blind design the drug or a placebo was given orally in three divided doses over a 24 hour period. Four dose levels (750 mg, 1000 mg, 1250 mg and 1500 mg) were studied. Eight healthy male volunteers were enrolled in the study at each dose level. Although mild symptoms of drug intolerance occurred in some subjects, division of the drug dose into 3 oral administrations effectively doubled drug tolerance over the single oral dose administration.

Experiment #18, WR 194,965 H₃PO₄: Safety and Tolerance to Three Divided Doses, Rising Dose Levels, was implemented during the reporting period. The protocol for this study is presented in this report. In previous studies of safety and tolerance of the drug in man, the greatest tolerated single oral dose (mg/kg) was less than the dose that has cured 100% of Aotus monkeys infected with falciparum malaria. In order to determine if greater tolerance could be achieved with divided doses, WR 194,965 H₃PO₄ or a placebo was given in three divided doses over a 24 hour period. During the reporting period, three dose levels (1000 mg, 1250 mg and 1500 mg) were studied. Four healthy male volunteers were enrolled in the study at each dose level. The study was suspended in July, 1981, in order to pursue higher priority studies (Protopam Chloride). The results of that portion of Experiment #18 completed during the reporting period will be presented in the final clinical report.

FOREWORD

Phase I clinical studies of drugs under development by the U.S. Army Research and Development Command (USAMRDC) were performed at the clinical facility of BIO-MED, Inc. under the terms of the contract DAMD17-75-C-5036. All protocols were jointly reviewed by BIO-MED, Inc. and the Division of Experimental Therapeutics of the Walter Reed Army Institute of Research, and approved by the Institutional Review Board of BIO-MED, Inc. and the Human Subjects Research Review Board, Office of the Surgeon General, Department of the Army before implementation at BIO-MED, Inc.

Special assurance for the conduct of these studies has been extended from the Headquarters of the USAMRDC to BIO-MED, Inc.

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

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Tolerance to Three Divided Doses, Rising Dose Levels.

Distribution List

BIO - MED, Inc.

4401 HARTWICK ROAD . COLLEGE PARK MARYLAND 20740 . TELEPHONE: (202) 882-0977

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 17

TITLE: WR 180,409-H₃PO₄: SHORT TERM
MULTIPLE DOSES, SAFETY,
TOLERANCE AND PHARMACOKINETICS

PRINCIPAL INVESTIGATOR: JOHN A. JOHNSON, M.D.

CLINICAL DIRECTOR: KEVIN G. BARRY, M.D.

ASSOCIATE DIRECTOR: LESLIE B. ALTSTATT, M.D.

INSTITUTIONAL REVIEW GEORGE BANNING, JR., M.D., CHAIRMAN

BOARD MEMBERS: JAMES A. DUKE, Ph.D.

JOSEPH J. D'ERASMO, LL.B.

JUDY HANNAH

ANGELO J. TROISI

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 17

WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES, SAFETY,
TOLERANCE AND PHARMACOKINETICS

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FINAL CLINICAL REPORT

EXPERIMENT NUMBER 17

WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES, SAFETY,
TOLERANCE AND PHARMACOKINETICS

ABSTRACT

In a double-blind study of safety and tolerance, 32 healthy male subjects were each given from 750 to 1500 mg of the drug WR 180,409·H₃PO₄, or placebo, in 3 doses over a period of 24 hours. Blood specimens were collected at the designated times and sent to the Department of Pharmacology, Walter Reed Army Institute of Research, for determination of the pharmacokinetics of WR 180,409·H₃PO₄ in multiple doses.

Although mild gastrointestinal symptoms or lightheadedness were observed in one of every four subjects receiving the drug, there was no apparent dose/response relationship and equivalent symptoms were also encountered in subjects receiving placebo. No clear-cut signs of intolerance were noted at any dose level administered.

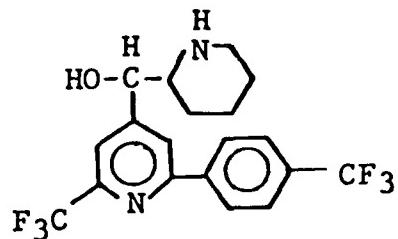
FINAL CLINICAL REPORT

EXPERIMENT NUMBER 17

WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES, SAFETY,
TOLERANCE AND PHARMACOKINETICS

INTRODUCTION

WR 180,409·H₃PO₄ is a 4-pyridinemethanol with the following structure:



It is being studied for its potential for curing chloroquine resistant falciparum malaria (Vietnamese-Smith strain) in man using a short term (24hr.) course of therapy.

Pre-clinical efficacy studies in mice showed that the drug cured malaria at 640 mg/kg. Studies in Aotus monkeys showed that 12 mg/kg per dose in 3 daily doses cured 5 of 5 animals infected with chloroquine resistant P. falciparum malaria (Vietnamese-Smith strain) and that doses of 5 mg/kg given daily for 7 days cured 8 of 8 Aotus monkeys similarly infected.

Pre-clinical toxicity studies showed that in mice and rats the acute LD₅₀'s were 900 mg/kg and 500 mg/kg respectively. However, single doses of 37 mg/kg frequently caused vomiting in beagle dogs. Thus, the curative dose for monkeys (about 35 mg/kg) was well below the LD₅₀ dose for rodents (500-900 mg/kg), but close to the amount producing vomiting in dogs (37 mg/kg) when given in a single dose.

In man, in Phase I clinical studies, 13 of 16 subjects who received 750 mg in a single oral dose (8.5 - 12.5 mg/kg) developed nausea and/or vomiting. Although these subjects developed no abnormal physical findings or laboratory values, it was considered inadvisable to attempt higher single doses of this formulation.

The present study was undertaken to determine whether multiple doses of the drug could be given over a 24 hour period, circumventing the undesirable gastro-intestinal effects while achieving a curative blood level of the drug.

In this study, subjects were observed for tolerance to 3 doses of the drug, while at the same time blood samples were taken so that the pharmacokinetics of the multiple doses could be determined. Previous studies in humans showed that a single 750 mg dose produced a mean peak level of 362 ng/ml*, a mean time of peak level of 13.2 hours, and a mean half-life of 6.9 days.

* With chloroquine resistant *P. falciparum* malaria (Vietnamese-Smith strain), 48.5 ng/ml inhibits parasite growth in vitro.

METHODS AND MATERIALS:

Subject Selection:

Thirty-two male subjects between the ages of 18 and 33 were recruited from the Washington, D.C. metropolitan area. Candidates were hired as temporary employees of BIO-MED, Inc.

Candidates for employment were medically evaluated to obtain the subjects for study. The medical evaluation included a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential counts, red blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH and total bilirubin.

Subject acceptability criteria were based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects were rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest x-ray. The presence of conditions which did not increase risk for the subjects or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes were not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean were cause for rejection. Deviations between 2 and 3 standard deviations from the mean were generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/dl would have caused rejection, whereas a serum sodium of 153 mEq/L of itself would not. Subjects were 50-100 kg body weight.

When doubt existed concerning acceptance of a subject for any reason, a decision was made following consultation with fellow investigators and other specialists, as appropriate. In this manner, questionable candidates were given full consideration and the integrity and ethics of the Research Team protected.

Qualified candidates were given a complete explanation of the background and procedures used in the study and all details of the protocol as it involved the individual subjects. They were interviewed in a group and individually in the presence of a clinical physician. Each participant was given the opportunity to ask questions. Following this,

at the individual interview, the consent form was read and if the clinical investigator believed the subject understood his participation adequately to give informed consent, the subject was permitted to sign the consent form. On study day 1, the subject reaffirmed his consent in writing prior to his participation.

Procedures:

The design of this experiment was a 2x2, double-blind, rising dose level design with one replicate group for each dose level. Thirty-two subjects were divided into 8 groups of 4 subjects each. In each group, by random assignment, 2 subjects received drug and 2 received placebo. Two groups of 4 subjects were used at each dose level. The following table outlines the dosing schedule.

WR 180,409 DRUG ADMINISTRATION SCHEDULE

Time and Doses (in mg) of Drug or Placebo

Group	1st dose	2nd dose	3rd dose	Total Dose
	Day 1 0800	Day 1 2000	Day 2 0800	
A	250	250	250	750
B	250	250	250	750
C	500	250	250	1000
D	500	250	250	1000
E	500	500	250	1250
F	500	500	250	1250
G	500	500	500	1500
H	500	500	500	1500

The drug was supplied by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, in the form of 250 mg tablets labelled "WR 180,409·H₃PO₄".

On study day 0, a Monday, each group entered the clinical facility at BIO-MED, Inc. in College Park, Maryland. On that day, the physical examination, laboratory tests and urinalysis were repeated to ensure the continued qualification of subjects. On Study day 1, at 0800, subjects received their first dose, then again at 2000, and finally at 0800 of study day 2. Twenty-four blood specimens were taken for drug assay, beginning just before the first dosing and ending on study day 21 (See Sampling Schedule for Drug Assay). On study day 2, the physical examination and laboratory tests were repeated. On study day 3, subjects remained under observation in the clinic. On study day 4, following physical examination and laboratory tests, subjects were discharged from the clinic by 1800. Subjects returned briefly on study days 5, 7, 9, 11, 14, 17 and 21 for the taking of blood specimens. Physical examinations and laboratory tests were conducted on days 7, 14 and 21, with day

21 being the last day of participation for each group. Subjects in the final group (group H), however, returned on day 22 because National Health Laboratories was closed on day 21.

The study plan is summarized in the following schematic:

SCHEMATIC STUDY PLAN

Multiple Oral Dose Administration of WR 180,409

Day of Study	0*	1*	2*	3*	4*	5	7	9	11	14	17	21
Day of Week	M	T	W	TH	F	SA	M	W	F	M	TH	M
Physical Exam	X		X		X					X		X
Interview	X	X	X	X	X	X	X			X		X
Vital Signs	X	X	X	X	X	X	X			X		X
Lab Tests ⁺	X		X		X		X			X		X
Dose			X---X									
Assay Sample ⁺⁺	X	X	X	X	X	X	X	X	X	X	X	X
Controlled environment												

⁺ glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium phosphate, cholesterol, triglyceride, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies were done as clinically indicated.

⁺⁺ See "Sampling Schedule for Drug Assay"

The twenty-four blood specimens for drug assay, consisting of 6 ml whole blood per sample, were taken according to the following schedule:

EXPERIMENT #17 SAMPLING SCHEDULE FOR DRUG ASSAY

Study Day	Spec.#	Time	Cumulative Time (Hrs)	Interval (Hrs)
M 0	--	--	--	--
T 1	1	0755	0	--
	2	1400	6	6
	3	1955	12	6
W 2	4	0200	18	6
	5	0755	24	6
	6	0900	25	1
	7	1000	26	1
	8	1200	28	2
	9	1400	30	2
	10	1600	32	2
	11	2000	36	4
	12	2400	40	4
	13	0800	48	8
	14	1800	58	10
	15	0600	70	12
F 4	16	1800	82	12
	17	1000	98	16
S 5	18	1200	100	2
	19	1200	148	48
W 9	20	1200	196	48
F 11	21	1200	244	48
M 14	22	1200	316	72
Th 17	23	1200	388	72
M 21	24*	1200	484	96

* Total blood drawn for assays = 144 ml

Special Procedures:

Diet:

WR 180,409 is highly soluble in lipids. Lipids taken by mouth may influence drug absorption and high concentration of blood lipids may interfere with extraction of drug from the blood.

For 12 hours preceding drug administration and for 12 hours following, all meals and snacks were high in carbohydrates and low in fat and protein. To document compliance, dietary records were maintained on each subject on study days 0-2 (inclusive).

Diet - High Carbohydrates, Low Fat, Low Protein:
No added fat. No meats with high fat content.

BREAKFAST	LUNCH	DINNER
As much fresh or canned fruit as de- sired	3 oz. lean meat 1 slice bread*	3 oz. lean meat 1 slice bread*
1 slice bread*	Potato (noodles, rice) 1/2 cup	1/2 cup potato (or substitute)
Cereal (3/4 cup dry or 1/2 cup cooked)	2 vegetables (1/2 cup each) - cooked in plain water	2 vegetables (1/2 cup each)
1 egg	As much fruit as desired	As much fruit as desired
8 oz. skim milk	Beverage	Beverage

MID-MORNING - MID-AFTERNOON - EVENING SNACKS

Sandwich (2 slices bread, 1 oz. lean meat).
As much fruit as desired.
Beverage

* Any item from bread exchange list (Menu Guide for Diabetes, Eli Lilly and Company, Indianapolis, Indiana) may be substituted.

Monitoring:

Individual work sheets were maintained on each subject. The following data was recorded according to the schematic study plan: pulse, temperature, blood pressure, weight, clinical and laboratory test results, diet, symptoms and pertinent physical findings. In addition, a specimen schedule was maintained for each subject to record exact times of dosing and blood sample collections.

RESULTS:

Compliance:

Compliance is depicted in the Appendix, Figures A-H. Thirty-two subjects were involved in the study, and all completed the study. There were no significant departures from protocol. No emergent or adverse events occurred requiring special care or disposition.

Symptoms:

Of the subjects receiving drug, one had a diminished appetite at the first dose level (750mg), one had a liquid stool 4 hours after the first dosing at the second dose level (1000mg), one had lightheadedness at the third dose level (1250mg), and one had dizziness and nausea at the fourth dose level (1500mg).

Abdominal pain occurred in 3 subjects receiving placebo. One had nausea and vomiting 6 days after discharge.

Symptoms are further detailed in the Individual Subject Final Summaries.

Laboratory Results:

Laboratory abnormalities in both the drug and placebo groups were minimal and inconsistent. No pattern of abnormality emerged suggesting drug effect. SGOT and SGPT elevations occurred with equal frequency in the drug and placebo groups.

Significant laboratory results are tabulated in the individual subject summaries in the Appendix.

DISCUSSION:

The clinical portion of this study was designed to see if administration of the drug in divided doses would eliminate the gastrointestinal symptoms seen consistently in previous studies when the drug was given in a single 750 mg dose. That question is answered affirmatively. In this study, symptoms which might be ascribed to the drug were mild and not debilitating. Since there was not a dose/response relationship between amount of drug and severity of symptoms seen, and since equivalent symptoms occurred in the placebo group, the association between drug and symptoms is questionable.

Laboratory abnormalities seen in this study were not noteworthy except for the SGOT and SGPT elevations which occurred with equal frequency in the drug and placebo groups. The reasons for SGOT and SGPT not being under good experimental control are presently under investigation.

CONCLUSIONS AND RECOMMENDATIONS:

In this study, WR 180,409-H₃PO₄ was given in a double-blind, rising dose schedule in amounts of 750 mg, 1000mg, 1250mg and 1500mg in three divided doses to 16 healthy human subjects. In the clinical portion of this study, mild, inconsistent symptoms which could be related to drug administration occurred in 1 of 4 subjects at each drug level. By dividing this drug into 3 doses, the tolerance was effectively doubled over the previously established single oral dose. Pharmacokinetics of this drug will be reported subsequently when those data are available. Presently, there is no clinical contraindication to the administration of this drug to human subjects in amounts up to 1500 mg in 24 hours in 3 divided doses.

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EXPLANATION FOR POTENTIAL SUBJECTS

EXPERIMENT #17

WR 180,409·H₃PO₄*: SAFETY, TOLERANCE AND PHARMACOKINETICS**
WITH SHORT TERM MULTIPLE DOSES.

Gentlemen:

The study for which you have volunteered involves taking by mouth the antimalarial drug named WR 180,409. This is one of many antimalarial drugs being developed by the U.S. Army Medical Service, the sponsor of this study, in an effort to improve the treatment of drug resistant malaria. WR 180,409 has been approved for clinical testing in humans by both the sponsor and the Food and Drug Administration.

In a previous study with humans, 13 of 16 subjects who received a single dose of 750 mg. by mouth developed nausea and/or vomiting. Such reactions make administration of the drug in a single dose impractical. In this study, for which you are being considered, WR 180,409 will be administered in 3 doses of 250-500 mg. of the drug over a period of 24 hours in an attempt to avoid the undesirable clinical effects.

In order to monitor the safety of the drug, your tolerance to the drug, and the rate at which the drug builds up in the blood during this study, we will conduct interviews, physical examinations, blood tests for the level of the drug and its effects on you, urine tests, and measurements of your vital signs. These are summarized on the following page.

* WR 180,409·H₃PO₄ will be hereinafter designated as WR 180,409.

** Pharmacokinetics is the study of bodily absorption, distribution, metabolism and excretion of drugs.

SCHEMATIC STUDY PLAN

Multiple Oral Dose Administration of WR 180,409

Day of Study	0*	1*	2*	3*	4*	5	7	9	11	14	17	21
Day of Week	M	T	W	TH	F	SA	M	W	F	M	TH	M
Physical Exam	X		X		X							X
Interview	X	X	X	X	X	X	X			X		X
Vital Signs	X	X	X	X	X	X	X			X		X
Lab Tests ⁺	X		X		X		X			X		X
Dose			X---X									
Assay Sample ⁺⁺	X	X	X	X	X	X	X	X	X	X	X	X

* Controlled environment

+ glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglyceride, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

++ See "Sampling Schedule for Drug Assay"

WR 180,409 DRUG ADMINISTRATION SCHEDULE

Time and Doses (in mg) of Drug or Placebo

Group	1st dose	2nd dose	3rd dose	Total Dose
	Day 1	Day 1	Day 2	
	0800	2000	0800	
A	250	250	250	750
B	250	250	250	750
C	500	250	250	1000
D	500	250	250	1000
E	500	500	250	1250
F	500	500	250	1250
G	500	500	500	1500
H	500	500	500	1500

EXPERIMENT #17 SAMPLING SCHEDULE FOR DRUG ASSAY

Study Day	Spec.#	Time	Cumulative Time	Interval Time
M 0	--	--	--	--
T 1	1	0755	0	--
	2	1400	6	6
	3	1955	12	6
W 2	4	0200	18	6
	5	0755	24	6
	6	0900	25	1
	7	1000	26	1
	8	1200	28	2
	9	1400	30	2
	10	1600	32	2
	11	2000	36	4
	12	2400	40	4
Th 3	13	0800	48	8
	14	1800	58	10
F 4	15	0600	70	12
	16	1800	82	12
S 5	17	1000	98	16
	18	1200	100	2
M 7	19	1200	148	48
W 9	20	1200	196	48
F 11	21	1200	244	48
M 14	22	1200	316	72
Th 17	23	1200	388	72
M 21	24*	1200	484	96

* Total blood drawn for assays = 144 ml

At your discretion a small teflon catheter can be placed in one of your arm veins 15 minutes before drug administration. This will be used to obtain blood samples during the day you are dosed. In this way, repeated venipuncture may not be necessary on that day.

It is important that the blood be obtained at the times specified. On the days you come in for blood drawing, it is important that if you eat, it should be a light meal, (i.e., cereal, juice, coffee, bread - no milk or fatty foods because fat in the blood makes it more difficult to measure the drug). It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol. Such factors as time of day, meals, alcohol, other drugs and lack of proper sleep may affect the level of drug in your blood on any given day.

You must understand the risks to which you will be exposed in the course of this study. There are the risks, discomforts and inconveniences of residing in a clinical facility for a few days, and having routine measurements and venipunctures performed. In this study, there is a chance that you will develop nausea, vomiting, or abdominal discomfort. It is our expectation that if these symptoms develop, they will be minor and of short duration, and have no lasting effect upon your health. Finally, there is always the possibility of unexpected reactions to the drug. That possibility is minimal, but it should be taken into account.

You should know the policies and procedures followed at BIO-MED, Inc. to minimize the risk to your health and well-being. They are:

1. All procedures are conducted by a physician licensed in Maryland, or by a registered nurse or technician directly under the physician's supervision.
2. Each study to be conducted at BIO-MED, Inc. is reviewed by other agencies for compliance with Department of Health and Welfare Guidelines regarding volunteer participation in medical experiments. Those agencies are:
 - a. The Food and Drug Administration. This arm of the Federal Government reviews study proposals for investigational new drugs.
 - b. The Regulatory Agencies of the sponsoring bodies. In the case of studies sponsored by the U.S. Army, studies must be approved by the Human Use Committee of the Office of the Surgeon General of the U.S. Army.

- c. The Institutional Review Board of BIO-MED, Inc.
This board is made up of informed citizen's from the local community. The board reviews each proposed study to see that the risks to the subjects are minimal, that precautions are taken to avoid risk when possible, and that risks are fully disclosed to the subject. The members of this board occasionally visit the clinical facility to inspect the conduct of a study.
- 3. To further insure your personal protection the following standard procedures are established:
 - a. Should you require emergency medical treatment you will be taken to nearby Doctor's Hospital of Prince Georges' County.
 - b. As a temporary employee of BIO-MED, Inc., you are protected by Workmen's Compensation for disability resulting by reason of your employment.
 - c. On your final day of participation, a complete physical examination and laboratory evaluation will be conducted. You will be informed of any abnormal findings, and should there be any, we will follow you until normalcy, stabilization or proper medical disposition is assured.

After members of the investigating team have interviewed you individually and are satisfied that you understand the study and the written informed consent form you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent form, you signify that the study has been explained to you with regard to risks and requirements and that you wish to participate.

It should be clear to you that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to individuals who travel to these areas. Your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent and your participation at anytime without prejudice to yourself.

SUBJECT AGREEMENT
CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled "WR 180,409·H₃PO₄: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. _____, and are set forth in the document titled "Explanation for Potential Subjects, Experiment Number 17: WR 180,409·H₃PO₄: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics.", which I have initialed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study. I also understand that my participation may be as a control subject.

I understand that as a temporary employee of BIO-MED, Inc. that Workmen's Compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at anytime; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

Date _____

Signature _____

Investigator Certification _____

Address _____

Witness _____

REAFFIRMATION OF CONSENT:

Date _____

Witness _____

Signature _____

BMI-300

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 452 GROUP: A AGE: 20 WEIGHT: 64.54 kg HEIGHT 170.18

DOSING DATE:	1st Dosing <u>3/3/81</u>	2nd Dosing <u>3/3/81</u>	3rd Dosing <u>3/4/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>3.87</u>	<u>3.87</u>	<u>3.87</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/25	3/2	3/3	3/4	3/5	3/6	3/9	3/16	3/23
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X			X	X	X
5. CBC	X			X					

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Sodium	139	142	140	140	139	140	136L	137-151 mEq/L
Uric Acid	7.4	8.1H	6.4	6.4	7.7	8.3H	7.2	4-8 mg/dl
T. Protein	8.1H	7.7	8.3H	7.8	8.2H	8.4H	7.9	6.4-8.0 g/dl
Albumin	5.0	4.7	5.0	4.7	4.9	5.3H	4.9	4.1-5.1 g/dl
HCT	51.1H	45.9	51.8H	48.3	49.6	48.5	49.2	40-50 Vol %
HgB	17.2H	15.8	17.7H	16.5	16.6	16.5	16.5	13.3-16.7 GMS %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 453 GROUP: A AGE: 20 WEIGHT: 64.09 kg HEIGHT 172.72

DOSING DATE:	<u>1st Dosing</u> <u>3/3/81</u>	<u>2nd Dosing</u> <u>3/3/81</u>	<u>3rd Dosing</u> <u>3/4/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>3.90</u>	<u>3.90</u>	<u>3.90</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/26	3/2	3/3	3/4	3/5	3/6	3/9	3/16	3/23
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X	X	X	X
5. CBC	X			X		X	X	X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	86	82	79	87	105	79	118H	66-114 mg/dl
Sodium	141	143	141	141	139	138	136L	137-151 mEq/L
Phosphate	3.4	3.1	4.2	4.7H	2.9	2.6	2.7	2.5-4.5 mg/dl
Triglycerides	198	161	201	83	135	239H	141	0-207 mg/dl
Alka. Phos.	102H	98H	101H	97H	102H	89	107H	26-94 U/L
WBC	11.8H	9.5	11.4H	11.0H	8.2	8.9	10.3H	3.1-9.5 10 ³ /ml
Retic.Count	N.D.	0.5	1.2	1.0	0.9	2.1H	1.1	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 454 GROUP: A AGE: 33 WEIGHT: 72.27 kg HEIGHT 175.26

DOSING DATE:	<u>3/3/81</u>	1st Dosing	<u>3/3/81</u>	2nd Dosing	<u>3/4/81</u>	3rd Dosing	<u>3/4/81</u>
TIME DOSED:	<u>0800</u>		<u>2000</u>		<u>0800</u>		<u>0</u>
DOSE (mg/kg):	<u>0</u>		<u>0</u>		<u>0</u>		<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/25	3/2	3/3	3/4	3/5	3/6	3/9	3/16	3/23
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X	X	X	X
5. CBC		X							X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Albumin	4.7	4.5	4.5	4.8	5.0	5.3H	4.9	4.1-5.1 g/dl
Alka. Phos.	96H	99H	97H	108H	98H	96H	96H	26-94 U/L
SGOT	22	20	16	34	76H	27	20	0-47 U/L
SGPT	15	18	21	46	122H	53H	22	0-47 U/L
MCH	31.8	32.4	31.8	32.4	31.6	31.9	33.1H	27-33 G
Retic.Count	N.D.	0.4L	0.7	1.1	1.2	1.4	0.9	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Alkaline phosphatase was elevated for the duration of the study and seems to be a normal deviation for this subject. SGOT was elevated 76 Day 7 and was normal on Day 14. SGPT was elevated 122 Day 7, 53 Day 14 and was normal on Day 21.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 455 GROUP: A AGE: 24 WEIGHT: 60.45 kg HEIGHT 170.18

DOSING DATE:	<u>1st Dosing</u> <u>3/3/81</u>	<u>2nd Dosing</u> <u>3/3/81</u>	<u>3rd Dosing</u> <u>3/4/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/25	3/2	3/3	3/4	3/5	3/6	3/9	3/16	3/23
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X	X	X	
5. CBC		X				X			

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	95	76	74	89	71	58L	86	66-114 mg/dl
Creatinine	1.2	1.4	1.0	1.2	1.5H	1.2	1.2	0.8-1.4 mg/dl
Uric Acid	5.6	5.5	5.8	5.1	6.9	8.1H	5.8	4-8 mg/dl
T. Protein	8.4H	8.1H	7.2	7.3	7.3	7.1	7.5	6.4-8.0 g/dl
Alka. Phos.	105H	111H	103H	114H	103H	85	82	26-94 U/L
SGPT	12	14	16	86H	27	7	11	0-47 U/L
LDH	240H	244H	186	203	230	158	194	72-233 U/L
MCV	82	83	83	81L	82	83	85	82-98
Retic.Count	N.D.	0.3L	1.2	0.9	1.0	1.2	0.9	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not related to the study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 456 GROUP: B AGE: 19 WEIGHT: 63.64 kg HEIGHT 171.45

DOSING DATE:	1st Dosing <u>3/10/81</u>	2nd Dosing <u>3/10/81</u>	3rd Dosing <u>3/11/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>3.93</u>	<u>3.93</u>	<u>3.93</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/3	3/9	3/10	3/11	3/12	3/13	3/16	3/23	3/30
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms				X	X				
2. Physical Exam						X			X
3. Urinalysis									
4. Biochemistry	X			X		X			
5. CBC				X					

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Sodium	138	139	139	136L	138	137	140	137-151 mEq/L
Uric Acid	3.4L	4.0	3.6L	3.4L	5.2	5.2	5.5	4-8 mg/dl
SGPT	11	19	30	53H	33	21	15	0-47 U/L
WBC	8.6	7.3	10.9H	8.7	7.2	7.9	6.9	3.1-9.5 10 ³ /ml

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: Two hours after third dosing the subject complained of cold symptoms which lasted about 48 hours. He remained afebrile. Physical exam showed tender nodes Day 4 and few rhonchi in left chest Day 21.

ABNORMALITIES COMMENT: SGPT was 53 Day 4 and returned to normal Day 7. Other laboratory abnormalities were minimal and inconsistent and not considered study related.

CONCLUSION: Elevated SGPT possibly related to ingestion of drug.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 457 GROUP: B AGE: 22 WEIGHT: 79.09 kg HEIGHT 184.15

DOSING DATE:	<u>1st Dosing</u> <u>3/10/81</u>	<u>2nd Dosing</u> <u>3/10/81</u>	<u>3rd Dosing</u> <u>3/11/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/26	3/9	3/10	3/11	3/12	3/13	3/16	3/23	3/30
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms			X						
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X	X	X	
5. CBC									

KEY: X=abnormal *controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	85	79	88	85	88	117H	82	66-114 mg/dl
Creatinine	0.8	0.7L	1.3	0.9	1.1	1.1	0.9	0.8-1.4 mg/dl
Sodium	136L	137	141	138	140	136L	139	137-151 mEq/L
T. Protein	7.3	7.6	8.3H	7.2	7.9	7.7	7.5	6.4-8.0 g/dl
Phosphate	2.6	4.2	3.4	4.8H	3.2	2.9	3.1	2.5-4.5 mg/dl
Triglycerides	94	112	242H	187	79	59	73	0-207 mg/dl
SGPT	21	20	23	40	53H	14	22	0-47 U/L

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: Five hours after third dosing the subject complained of a slight dry throat. He was asymptomatic for the rest of the study. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal and inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 458 GROUP: B AGE: 24 WEIGHT: 78.18 kg HEIGHT 179.07

DOSING DATE:	1st Dosing <u>3/10/81</u>	2nd Dosing <u>3/10/81</u>	3rd Dosing <u>3/11/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/3	3/9	3/10	3/11	3/12	3/13	3/16	3/23	3/30
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms				X					
2. Physical Exam									
3. Urinalysis								X	
4. Biochemistry		X		X		X	X	X	X
5. CBC	X	X					X	X	

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
BUN	10	7L	8L	9	13	7L	8L	9-21 mg/dl
T. Protein	7.2	7.0	6.7	6.1L	6.9	6.6	6.7	6.4-8.0 g/dl
Phosphate	3.0	1.8L	3.7	4.2	3.1	1.8L	2.3L	2.5-4.5 mg/dl
SGPT	34	40	42	35	50H	20	28	0-47 U/L
HCT	51.1H	50.6H	46.1	44.9	46.3	44.6	45.2	40-50 Vol %
HgB	17.7H	16.9H	16.0	15.5	16.1	15.5	15.1	13.3-16.7 GMS %
Lymphs	20	25	30	34	22	17L	21	19-59 %
UA - Protein	7	6	5	5	6	6	8H	5-7
Retic.Count	N.D.	1.6H	1.1	1.2	1.2	1.0	2.4H	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: Eleven hours after third dosing the subject became nauseated and vomited about half of the dinner he had just finished eating. He was asymptomatic for the rest of the study. The physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered to be related to the study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 459 GROUP: B AGE: 19 WEIGHT: 74.09 kg HEIGHT 194.31

DOSING DATE:	<u>3/10/81</u>	1st Dosing	<u>3/10/81</u>	2nd Dosing	<u>3/10/81</u>	3rd Dosing	<u>3/11/81</u>
TIME DOSED:	<u>0800</u>		<u>2000</u>		<u>0800</u>		<u>0800</u>
DOSE (mg/kg):	<u>3.37</u>		<u>3.37</u>		<u>3.37</u>		<u>3.37</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/26	3/9	3/10	3/11	3/12	3/13	3/19	3/23	3/30
STUDY DAY:	Screen	0*	1*	2*	3*	4*	10	14	21
1. Symptoms		X							
2. Physical Exam									
3. Urinalysis						X			
4. Biochemistry	X	X		X		X	X	X	X
5. CBC			X						X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	84	74	87	92	55L	75	117H	66-114 mg/dl
BUN	11	11	10	7L	9	10	9	9-21 mg/dl
Sodium	136L	138	139	136L	142	138	138	137-151 mEq/L
Alka. Phos.	90	97H	99H	96H	84	88	85	26-94 U/L
LDH	189	239H	192	172	215	254H	180	72-233 U/L
RBC	5.63	5.62	5.82H	5.50	5.20	4.99	5.08	4.3-5.7 10 ³ /ml
UA - WBC	2	5	Neg	TNTC/ clumps H	Occ	Neg	3	0-5
Retic.Count	N.D.	0.5	1.0	0.9	0.9	1.0	1.6H	0.5-1.5 %

KEY: H - high L - low ND - not done Neg - negative TR - trace
Occ - occasional TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On the first day of dosing the subject stated he had a slight decrease in appetite; he ate most of the food that was served. He was asymptomatic for the remainder of the study. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: Lack of appetite possible due to drug ingestion.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: <u>460</u>	GROUP: <u>C</u>	AGE: <u>20</u>	WEIGHT: <u>79.54</u> kg	HEIGHT <u>176.53</u>
DOSING DATE:	1st Dosing <u>3/17/81</u>		2nd Dosing <u>3/17/81</u>	
TIME DOSED:	<u>0800</u>		<u>2000</u>	
DOSE (mg/kg):	<u>6.29</u>		<u>3.14</u>	

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/3	3/16	3/17	3/18	3/19	3/20	3/23	3/30	4/6
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis						X			
4. Biochemistry				X				X	X
5. CBC	X					X	X	X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Potassium	4.7	5.0	4.7	4.5	4.7	5.4H	4.9	3.6-5.2 mEq/L
T. Protein	7.9	7.4	7.8	7.6	8.1H	8.2H	7.1	6.4-8.0 g/dl
Albumin	5.0	4.8	4.9	4.9	5.3H	5.2H	4.7	4.1-5.1 g/dl
LDH	202	188	234H	170	198	170	186	72-233 U/L
WBC	13.0H	9.2	7.6	8.9	14.1H	7.3	11.9H	3.1-9.5 10 ³ /ml
UA - Protein	Neg	Neg	Neg	Tr H	Neg	Neg	Neg	Negative
Retic.Count	N.D.	0.7	0.7	3.7H	0.9	0.2L	0.7	0.5-1.5 %

KEY: H - high L - low ND - not done Neg - negative Tr - trace

SYMPTOMS AND PHYSICAL FINDINGS: The subject remained asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal and inconsistent and not considered study related.

CONCLUSION: No adverse effects from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 461 GROUP: C AGE: 18 WEIGHT: 88.64 kg HEIGHT 182.25

DOSING DATE:	1st Dosing <u>3/17/81</u>	2nd Dosing <u>3/17/81</u>	3rd Dosing <u>3/18/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>5.64</u>	<u>2.82</u>	<u>2.82</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/10	3/16	3/17	3/18	3/19	3/20	3/23	3/30	4/6
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis				X					
4. Biochemistry	X	X		X		X	X	X	X
5. CBC				X					X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	72	90	53L	84	71	95	85	66-114 mg/dl
Potassium	4.0	4.1	4.3	4.1	4.2	4.0	3.3L	3.6-5.2 mEq/L
Chloride	100	98	96L	101	102	102	98	98-110 mEq/L
Uric Acid	4.8	3.7L	4.8	4.8	5.3	5.6	5.0	4-8 mg/dl
Alka. Phos.	117H	104H	122H	110H	107H	98H	104H	26-94 U/L
LDH	251H	231	222	240H	225	221	243H	72-233 U/L
HCT	49.2	46.6	51.8H	49.7	45.2	45.9	48.4	40-50 Vol. %
HgB	15.8	16.1	17.5H	16.5	15.4	15.8	16.8H	13.3-16.7 GMS %
RBC	5.45	5.28	5.71H	5.47	4.99	5.17	5.38	4.3-5.7 10 ³ /ml
UA - PH	6	7	8H	6	7	6	7	5-7

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Alkaline phosphatase remained elevated throughout the study which is normal for the subject's age. All other laboratory abnormalities were minimal and inconsistent and not considered related to the study.

CONCLUSION: No adverse effects from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 462 GROUP: C AGE: 19 WEIGHT: 76.82 kg HEIGHT 184.78

DOSING DATE:	1st Dosing <u>3/17/81</u>	2nd Dosing <u>3/17/81</u>	3rd Dosing <u>3/18/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/3	3/16	3/17	3/18	3/19	3/20	3/23	3/30	4/6
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms				X					
2. Physical Exam						X			
3. Urinalysis									
4. Biochemistry	X	X		X		X	X	X	X
5. CBC	X	X		X					

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	92	82	83	88	135H	57L	96	66-114 mg/dl
BUN	10	10	8L	8L	12	10	10	9-21 mg/dl
Alka. Phos.	101H	113H	110H	112H	111H	95H	105H	26-94 U/L
HCT	48.2	45.6	50.2H	46.0	45.3	44.4	44.4	40-50 Vol. %
HgB	17.0H	16.1	17.4H	15.8	16.1	15.9	15.8	13.3-16.7 GMS %
RBC	5.71H	5.45	5.86H	5.35	5.31	5.29	5.29	4.3-5.7 10 ³ /ml
Lymphs	25	27	22	24	19	24	17L	19-59 %
Monos	8	10	8	8	4	10	14H	0-10 %
Retic.Count	N.D.	0.4L	1.0	0.6	0.9	1.1	0.9	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: About 6 1/2 hours after second dosing subject had upper to midabdominal cramping which lasted about 1/2 hour and ceased spontaneously. Forty-five minutes after third dosing he complained of upper to midabdominal cramping which lasted about 3 hours and was relieved by the passage of gas. He continued to have slight "tightness" of upper abdomen for about 12 more hours. No further symptoms occurred until Day 4 of the study when he noted he had a fine erythematous rash on his chest. A week later on physical exam he had blanching erythematous macular rash of his upper extremities and trunk. He was referred to a dermatologist for consultation. Diagnosis: Pityriasis rosea. A week later the rash was dry and scaling. He was asymptomatic for the rest of the study. The close-out physical exam was normal.

CODE: 462 (contd)

ABNORMALITIES COMMENT: Alkaline phosphatase was consistently elevated. This is normal for this subject's age. All other laboratory abnormalities were minimal or inconsistent and not considered related to the study.

CONCLUSION: No adverse effects from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 463 GROUP: C AGE: 24 WEIGHT: 80.45 kg HEIGHT 181.61
DOSING DATE: 3/17/81 1st Dosing 2nd Dosing 3rd Dosing
TIME DOSED: 0800 2000 0800
DOSE (mg/kg): 0 0 0

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/10	3/16	3/17	3/18	3/19	3/20	3/23	3/30	4/6
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam				X	X	X	X		
3. Urinalysis						X			
4. Biochemistry	X	X		X		X	X	X	
5. CBC	X			X		X			X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	103	84	79	163H	147H	132H	80	66-114 mg/dl
BUN	14	12	8L	13	16	14	12	9-21 mg/dl
Creatinine	1.3	1.3	1.3	1.4	1.5H	1.4	1.2	0.8-1.4 mg/dl
T. Protein	5.9L	6.2L	5.9L	6.2L	6.2L	5.8L	6.4	6.4-8.1 g/dl
Albumin	4.1	4.2	4.1	4.2	4.2	3.9L	4.3	4.1-5.1 g/dl
Eosin	7H	5	6H	7H	5	5	6H	0-5 %
UA - WBC	Neg	Rare	Neg	7H	Neg	Neg	Neg	0-5

KEY: H - high L - low ND - not done Neg - Negative

SYMPTOMS AND PHYSICAL FINDINGS: Thirty minutes after third dosing the subject complained of blurred vision. Physical exam showed conjunctivitis which lasted about 8 days. Throat culture during this time was negative. No other symptoms were reported.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 464 GROUP: D AGE: 18 WEIGHT: 82.73 kg HEIGHT 180.34

DOSING DATE:	<u>1st Dosing</u> <u>3/24/81</u>	<u>2nd Dosing</u> <u>3/24/81</u>	<u>3rd Dosing</u> <u>3/25/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>6.04</u>	<u>3.02</u>	<u>3.02</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/3	3/23	3/24	3/25	3/26	3/27	3/31	4/6	4/13
STUDY DAY:	Screen	0*	1*	2*	3*	4*	8	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X			X		X	X	X	X
5. CBC									

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
BUN	9	12	11	17	11	6L	6L	9-21 mg/dl
Sodium	138	138	138	136L	142	140	142	137-151 mEq/L
Uric Acid	6.7	6.9	6.7	6.4	8.2H	6.1	6.6	4-8 mg/dl
T. Protein	8.1H	7.3	8.1H	7.7	7.6	7.3	7.3	6.4-8.0 g/dl
Phosphate	2.9	4.4	3.8	5.0H	3.5	3.5	4.0	2.5-4.5 mg/dl
T. Bilirubin	1.0	0.7	1.8H	0.7	1.5H	0.5	0.8	0.0-1.3 mg/dl
Retic.Count	N.D.	1.1	1.6H	1.1	0.6	1.2	0.8	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered related to study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 465 GROUP: D AGE: 35 WEIGHT: 77.27 kg HEIGHT 173.99
DOSING DATE: 3/24/81 1st Dosing 2nd Dosing 3/24/81 3rd Dosing 3/25/81
TIME DOSED: 0800 2000 0800
DOSE (mg/kg): 0 0 0

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/10	3/23	3/24	3/25	3/26	3/27	3/30	4/6	4/13
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam								X	
3. Urinalysis									
4. Biochemistry	X					X	X	X	X
5. CBC		X		X		X		X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
BUN	9	9	11	12	8L	7L	10	9-21 mg/dl
Phosphate	3.3	4.0	3.8	4.7H	3.9	3.7	4.2	2.5-4.5 mg/dl
Alka. Phos.	95H	85	87	83	84	98H	110H	26-94 U/L
MCV	98	99H	99H	98	97	97	95	82-98
MCH	31.9	33.2H	33.5H	33.3H	32.9	33.5H	32.4	27-33 G
Retic.Count	N.D.	0.9	0.8	0.9	0.8	0.8	0.4L	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic except for a recurrence of old acne problems. Physical exam was normal and remained unchanged except for few fine pustular comedones last week of study.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409-H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 466 GROUP: D AGE: 29 WEIGHT: 74.09 kg HEIGHT 179.70

DOSING DATE:	<u>3/24/81</u>	1st Dosing	<u>3/24/81</u>	2nd Dosing	<u>3/25/81</u>	3rd Dosing	<u>3/25/81</u>
TIME DOSED:	<u>0800</u>		<u>2000</u>		<u>0800</u>		<u>3.37</u>
DOSE (mg/kg):	<u>6.75</u>						<u>3.37</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/17	3/23	3/24	3/25	3/26	3/27	3/30	4/6	4/13
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms		X	X					X	
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X			X		X	X		X
5. CBC									

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
BUN	7L	9	8L	9	7L	9	6L	9-21 mg/dl
T. Protein	7.4	6.5	8.2H	7.3	7.5	7.0	7.0	6.4-8.0 g/dl
Albumin	4.9	4.4	5.5H	4.7	4.9	4.8	4.5	4.1-5.1 g/dl
Phosphate	2.7	3.1	3.3	4.8H	3.1	2.9	3.4	2.5-4.5 mg/dl

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject had a liquid stool 4 hours after the first dosing and a queasy stomach which lasted for about 6 hours. The next morning after the third dosing he briefly complained of mild gastrointestinal distress after eating breakfast. On Day 14 he complained of right chest pain upon deep inspiration. This was not severe and lasted on and off for about 1 week. Chest x-ray was obtained and was negative. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered related to the study.

CONCLUSION: Gastrointestinal symptoms possibly related to drug ingestion.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 467 GROUP: D AGE: 23 WEIGHT: 64.09 kg HEIGHT 169.55

	1st Dosing	2nd Dosing	3rd Dosing
DOSING DATE:	<u>3/24/81</u>	<u>3/24/81</u>	<u>3/25/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/10	3/23	3/24	3/25	3/26	3/27	3/30	4/6	4/13
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis							X		
4. Biochemistry				X					
5. CBC	X						X	X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Potassium	4.2	4.4	5.7H	4.2	3.8	3.9	4.2	3.6-5.2 mEq/L
LDH	177	144	500H	123	138	151	147	72-233 U/L
WBC	8.8	5.5	6.6	7.7	5.2	9.4	9.6H	3.1-9.5 10 ³ /ml
Lymphs	12L	29	27	31	22	11L	14L	19-59 %
Monos	8	7	10	7	11H	8	7	0-10 %
UA - PH	5	7	6	5	8H	7	6	5-7

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409-H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 468 GROUP: E AGE: 19 WEIGHT: 78.18 kg HEIGHT 185.42

DOSING DATE:	<u>1st Dosing</u> <u>3/31/81</u>	<u>2nd Dosing</u> <u>3/31/81</u>	<u>3rd Dosing</u> <u>4/1/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/17	3/30	3/31	4/1	4/2	4/3	4/6	4/13	4/20
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms						X			
2. Physical Exam									
3. Urinalysis									
4. Biochemistry		X				X		X	
5. CBC		X					X		

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	105	60L	89	91	68	109	109	66-114 mg/dl
Phosphate	3.4	4.5	4.4	5.2H	3.4	3.2	3.8	2.5-4.5 mg/dl
Triglycerides	68	129	150	105	62	263H	91	0-207 mg/dl
HCT	41.3	40.2	44.7	40.2	39.8L	41.0	41.3	40-50 Vol. %
HgB	13.9	13.2L	15.1	13.4	13.3	13.7	13.7	13.3-16.7 GMS %
Lymphs	30	18L	40	41	24	22	27	19-59 %
Retic.Count	N.D.	0.3L	0.8	0.7	1.0	1.2	0.7	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: On the morning of Day 4 of the study the subject complained of a "sharp" pain right lower quadrant of the abdomen. He had just finished a large breakfast and was playing a vigorous game of ping-pong. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered related to study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 469 GROUP: E AGE: 24 WEIGHT: 60.45 kg HEIGHT 170.18

DOSING DATE:	<u>1st Dosing</u> <u>3/31/81</u>	<u>2nd Dosing</u> <u>3/31/81</u>	<u>3rd Dosing</u> <u>4/1/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/25	3/30	3/31	4/1	4/2	4/3	4/8	4/13	4/20
STUDY DAY:	Screen	0*	1*	2*	3*	4*	8*	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X	X		X
5. CBC	X	X		X				X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	95	92	87	80	63L	68	76	66-114 mg/dl
T. Protein	8.4H	7.7	8.5H	8.1H	7.2	7.6	7.0	6.4-8.0 g/dl
Albumin	5.0	4.5	4.9	4.7	4.2	4.3	4.0L	4.1-5.1 g/dl
Globulin	3.4	3.2	3.6H	3.4	3.0	3.3	3.0	1.8-3.4 g/dl
Phosphate	2.6	3.6	3.5	4.9H	3.3	3.8	3.0	2.5-4.5 mg/dl
Alka. Phos.	105H	99H	103H	102H	88	90	80	26-94 U/L
HCT	48.8	48.1	51.0H	46.5	**	44.2	40.8	40-50 Vol. %
HgB	16.6	15.6	17.5H	15.6	**	15.1	13.7	13.3-16.7 GMS %
RBC	5.91H	5.60	6.04H	5.52	**	5.34	4.85	4.3-5.7 10 ³ /ml
Eosin	3	6H	6H	5	**	9H	10H	0-5 %
Retic.Count	N.D.	0.6	1.1	0.9	**	0.5	0.3	0.5-1.5 %

KEY: H - high L - low ND - not done ** - clotted specimen

SYMPTOMS AND PHYSICAL FINDINGS: The subject remained asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered related to study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 470 GROUP: E AGE: 21 WEIGHT: 74.09 kg HEIGHT 172.09

DOSING DATE:	<u>1st Dosing</u> <u>3/31/81</u>	<u>2nd Dosing</u> <u>3/31/81</u>	<u>3rd Dosing</u> <u>4/1/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>6.75</u>	<u>6.75</u>	<u>3.37</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/17	3/30	3/31	4/1	4/2	4/3	4/6	4/13	4/20
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry				X		X		X	X
5. CBC			X		X	X	X		X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
BUN	11	9	8L	14	12	6L	11	9-21 mg/dl
Albumin	4.9	5.0	5.4H	5.1	4.6	4.6	4.8	4.1-5.1 g/dl
Phosphate	3.2	3.6	4.1	5.0H	3.2	3.3	3.4	2.5-4.5 mg/dl
SGOT	28	25	26	35	27	17	55H	0-47 U/L
LDH	209	173	206	200	178	167	259H	72-233 U/L
HCT	48.2	44.9	51.9H	49.0	42.8	45.9	46.8	40-50 Vol. %
HgB	15.9	14.6	17.4H	16.0	14.3	15.0	15.5	13.3-16.7 GMS %
RBC	5.52	5.08	5.90H	5.65	4.97	5.18	5.40	4.3-5.7 10 ⁶ /ml
WBC	7.1	6.0	8.1	9.8H	6.5	7.5	6.3	3.1-9.5 10 ³ /ml
Eosin	4	5	6H	6H	6H	5	7H	0-5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject remained asymptomatic for the duration of the study. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: SGOT was elevated to 55 and LDH was 259 Day 21. He was requested to return for repeat testing but elected not to come. Other abnormalities were minimal or inconsistent and not considered related to study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 471 GROUP: E AGE: 26 WEIGHT: 57.04 kg HEIGHT 140.97

DOSING DATE:	1st Dosing <u>3/31/81</u>	2nd Dosing <u>3/31/81</u>	3rd Dosing <u>4/1/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>8.77</u>	<u>8.77</u>	<u>4.38</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/17	3/30	3/31	4/1	4/2	4/3	4/6	4/13	4/20
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms				X					
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X		X	X
5. CBC	X			X					

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Uric Acid	3.9L	4.6	4.0	3.9L	4.2	4.1	3.8L	4-8 mg/dl
T. Protein	7.5	7.4	7.6	7.2	6.7	6.8	6.1L	6.4-8.0 g/dl
Albumin	5.4H	5.2H	5.2H	5.1	4.8	4.7	4.3	4.1-5.1 g/dl
Phosphate	2.3L	3.4	3.4	4.1	2.9	3.3	2.3L	2.5-4.5 mg/dl
Triglycerides	173	127	212H	126	172	232H	196	0-207 mg/dl
HCT	49.9	48.6	50.2H	47.1	45.9	46.4	44.3	40-50 Vol. %
HgB	16.9H	16.3	17.5H	16.1	15.9	16.0	15.1	13.3-16.7 GMS %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject complained of lightheadedness immediately after venipunctures twice the morning of the third dosing. He also complained of feeling "dopey, like on a narcotic" that same morning. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered related to the study.

CONCLUSION: Lightheadedness possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 472 GROUP: F AGE: 30 WEIGHT: 73.18 kg HEIGHT 168.91

DOSING DATE:	1st Dosing <u>4/7/81</u>	2nd Dosing <u>4/7/81</u>	3rd Dosing <u>4/8/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

PLACEBO

=====

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/17	4/6	4/7	4/8	4/9	4/10	4/13	4/20	4/27
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms		X	X						
2. Physical Exam									
3. Urinalysis									
4. Biochemistry		X		X			X	X	
5. CBC							X		X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Creatinine	1.3	1.6H	1.5H	1.4	1.2	1.5H	1.4	0.8-1.4 mg/dl
SGOT	29	34	22	11	60H	48H	23	0-47 U/L
SGPT	19	40	32	12	81H	61H	34	0-47 U/L
LDH	185	253H	198	175	233	315H	230	72-233 U/L
HCT	41.3	41.5	40.0	43.8	42.0	39.3L	41.5	40-50 Vol. %
HgB	13.7	13.7	13.4	14.7	13.7	13.0L	13.2L	13.3-16.7 GMS %
MCH	27.5	27.0	27.7	27.4	27.1	27.1	26.3L	27-33 G

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: About 6 hours after third dosing subject complained of vague abdominal discomfort "like gas" which decreased but was present for about 6 hours. He also complained of urinary frequency which lasted for about 24 hours on Days 1 and 2 of the study. Urinalysis and urine cultures were both normal. He was asymptomatic for the remainder of the study. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: SGOT and SGPT were elevated Days 7 and 14 and returned to normal Day 21. Other abnormalities were minimal and inconsistent and not considered related to study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 473 GROUP: F AGE: 20 WEIGHT: 75.91 kg HEIGHT 177.80

DOSING DATE:	1st Dosing <u>4/7/81</u>	2nd Dosing <u>4/7/81</u>	3rd Dosing <u>4/8/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>6.59</u>	<u>6.59</u>	<u>3.29</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/26	4/6	4/7	4/8	4/9	4/10	4/13	4/20	4/27
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis								X	
4. Biochemistry				X		X	X		
5. CBC					X	X			X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
CO ₂	24	25	22L	27	25	24	24	23-31 mEq/L
Albumin	4.7	4.8	4.6	5.2H	4.8	4.5	4.9	4.1-5.1 g/dl
Phosphate	2.6	3.2	4.3	6.0H	4.1	3.4	3.1	2.5-4.5 mg/dl
Triglycerides	95	97	224H	121	87	89	52	0-207 mg/dl
SGOT	20	16	20	19	48H	34	33	0-47 U/L
HCT	46.6	46.9	45.5	51.0H	44.2	42.2	45.6	40-50 Vol. %
HgB	15.9	15.9	15.6	17.4H	15.2	14.0	15.4	13.3-16.7 GMS %
WBC	6.2	7.4	9.5	9.1	8.2	6.9	13.4H	3.1-9.5 10 ³ /ml
Lymphs	29	22	23	35	13L	22	10L	19-59 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject remained asymptomatic throughout the study interval. The physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: SGOT was elevated 47 Day 7 and had returned to normal Day 14. All other abnormalities were minimal and inconsistent and not considered related to the study.

CONCLUSION: SGOT elevation possibly related to drug ingestion. No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409-H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 474 GROUP: F AGE: 18 WEIGHT: 73.18 kg HEIGHT 189.23

DOSING DATE:	1st Dosing <u>4/7/81</u>	2nd Dosing <u>4/7/81</u>	3rd Dosing <u>4/8/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>6.83</u>	<u>6.83</u>	<u>3.42</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/3	4/6	4/7	4/8	4/9	4/10	4/13	4/20	4/27
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X			X		X			
5. CBC				X			X	X	

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Potassium	4.5	4.6	3.5L	4.0	4.2	3.9	3.9	3.6-5.2 mEq/L
Chloride	99	102	104	97L	100	100	101	98-110 mEq/L
Phosphate	3.2	4.3	4.0	4.9H	4.5	4.2	3.9	2.5-4.5 mg/dl
Alka. Phos.	96H	91	95H	89	91	86	93	26-94 U/L
Eosin	2	4	6H	4	2	3	3	0-5 %
MCV	83	83	81L	83	81L	84	85	82-98
Platelets	230	186	200	183	206	75L	234	102-426 10 ³ /ml
Retic.Count	N.D.	0.9	0.7	1.3	0.7	1.3	2.0H	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. Physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Platelet count of 75,000 was reported Day 14 and was normal Day 21. This may represent a laboratory error. All other laboratory abnormalities were minimal and inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 475 GROUP: F AGE: 27 WEIGHT: 66.36 kg HEIGHT 168.91
DOSING DATE: 4/7/81 1st Dosing 2nd Dosing 3rd Dosing
TIME DOSED: 0800 2000 0800
DOSE (mg/kg): 0 0 0

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/24	4/6	4/7	4/8	4/9	4/10	4/13	4/20	4/27
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms							X		
2. Physical Exam							X		
3. Urinalysis							X		
4. Biochemistry	X	X		X			X	X	
5. CBC	X	X		X			X		

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	94	84	91	92	82	130H	81	66-114 mg/dl
Creatinine	1.4	1.6H	1.2	1.4	1.3	1.3	1.1	0.8-1.4 mg/dl
Potassium	4.1	4.3	3.8	4.0	4.2	3.4L	4.1	3.6-5.2 mEq/L
Chloride	98	102	97L	102	99	101	101	98-110 mEq/L
CO ₂	32H	29	28	30	33H	28	29	23-31 mEq/L
T. Bilirubin	1.4H	1.0	1.6H	0.9	0.9	1.1	1.3	0.0-1.3 mg/dl
HCT	50.9H	49.0	50.6H	48.7	47.4	45.4	47.7	40-50 Vol. %
HgB	17.7H	17.0H	17.8H	16.9H	16.8H	15.9	16.3	13.3-16.7 GMS %
UA - PH	5	5	5	6	8H	5	5	5-7

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: Six days after dosing, the subject woke up nauseated and vomited clear fluid 3 to 4 times before reporting for scheduled follow up visit. He was asymptomatic throughout the rest of the study. Physical exam showed hypoactive bowel sounds day of vomiting and was normal for the rest of the study.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered related to the study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 476 GROUP: G AGE: 23 WEIGHT: 66.59 kg HEIGHT 168.91
DOSING DATE: 4/14/81 1st Dosing 2nd Dosing 4/14/81 3rd Dosing 4/15/81
TIME DOSED: 0800 2000 0800
DOSE (mg/kg): 0 0 0

PLACEBO

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/24	4/13	4/14	4/15	4/16	4/17	4/20	4/27	5/4
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X			X		X			
5. CBC		X		X		X		X	

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	98	90	127H	93	101	111	90	66-114 mg/dl
Potassium	4.2	4.3	3.4L	4.1	3.8	4.2	4.3	3.6-5.2 mEq/L
Uric Acid	3.9L	4.7	5.1	3.9L	5.4	4.8	4.0	4-8 mg/dl
T. Protein	7.1	6.6	6.7	6.3L	7.1	7.3	7.4	6.4-8.0 g/dl
Phosphate	3.8	4.4	3.6	5.6H	3.7	3.5	3.5	2.5-4.5 mg/dl
Eosin	5	6H	6H	6H	4	6H	3	0-5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. The physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: The laboratory abnormalities were minimal or inconsistent and not considered related to the study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 477 GROUP: G AGE: 32 WEIGHT: 68.18 kg HEIGHT 168.91

DOSING DATE:	<u>4/14/81</u>	1st Dosing	<u>4/14/81</u>	2nd Dosing	<u>4/14/81</u>	3rd Dosing	<u>4/15/81</u>
TIME DOSED:	<u>0800</u>		<u>2000</u>		<u>0800</u>		
DOSE (mg/kg):	<u>0</u>		<u>0</u>		<u>0</u>		
PLACEBO							

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/24	4/13	4/14	4/15	4/16	4/17	4/20	4/27	5/4
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms				X					
2. Physical Exam									
3. Urinalysis									
4. Biochemistry					X	X			
5. CBC						X			X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
T. Protein	7.2	7.2	6.4	5.8L	6.6	7.0	6.7	6.4-8.0 g/dl
Albumin	4.9	4.9	4.1	3.9L	4.4	4.5	4.4	4.1-5.1 g/dl
Triglycerides	58	75	171	251H	274H	181	94	0-207 mg/dl
Retic.Count	N.D.	0.6	0.9	0.8	1.7H	1.5	1.9H	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: On second day of study the subject stated he had had a few brief episodes of dull pain over the right precordium which he had experienced before when anxious. He was asymptomatic for the remainder of the study interval. The physical exam was normal and remained unchanged for the duration of the study.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal and inconsistent and not considered related to the study.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 478 GROUP: G AGE: 22 WEIGHT: 79.09 kg HEIGHT 184.15

DOSING DATE:	<u>4/14/81</u>	1st Dosing	2nd Dosing	3rd Dosing
TIME DOSED:	<u>0800</u>		<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>6.32</u>		<u>6.32</u>	<u>6.32</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/26	4/13	4/14	4/15	4/16	4/17	4/20	4/27	5/4
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms				X					
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X	X	X	X
5. CBC				X		X	X		X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Sodium	136L	135L	137	137	136L	141	141	137-151 mEq/L
Chloride	101	97L	100	100	99	101	99	98-110 mEq/L
Uric Acid	5.8	6.9	6.4	6.3	8.6H	7.8	8.0	4-8 mg/dl
Albumin	4.5	4.3	3.9L	4.1	4.3	4.0L	4.3	4.1-5.1 g/dl
Globulin	2.8	2.9	3.0	3.2	3.4	3.4	3.6H	1.8-3.4 g/dl
Triglycerides	94	92	212H	144	97	122	128	0-207 mg/dl
Alka. Phos.	67	84	82	98H	110H	81	76	26-94 U/L
SGPT	21	15	32	64H	58H	27	29	0-47 U/L
LDH	149	190	207	239H	302H	233	189	72-233 U/L
WBC	7.9	6.0	7.4	8.8	10.7H	7.2	8.0	3.1-9.5 10 ³ /ml
Lymphs	26	44	78H	68H	61H	50	43	19-59 %
Segs	64	52	20L	22L	38	38	47	36-80 %
Retic.Count	N.D.	1.1	0.6	1.4	0.9	1.3	2.1H	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: Eleven hours and 45 minutes after third dosing subject complained of itching and erythematous patches were noted on elbows, knees and wrists which lasted about 3 hours and gradually disappeared. He was asymptomatic for the remainder of the study. Physical exam was normal and remained unchanged for the rest of the interval.

ABNORMALITIES COMMENT: Alkaline phosphatase was elevated 98 on Day 4, 110 Day 7, 97 Day 11 and had returned to normal Day 14. SGPT was elevated to 64 on Day 4, 58 Day 7 and returned to normal Day 14. LDH was elevated 239 on

Code # 478 (cont'd):

Day 4, 302 Day 7, 268 Day 11 and had returned to normal Day 14. Other abnormalities were minimal or inconsistent and not considered related to the study.

CONCLUSION: Enzyme elevations considered possibly drug related. No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409-H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 479 GROUP: G AGE: 20 WEIGHT: 63.64 kg HEIGHT 172.08

DOSING DATE:	<u>4/14/81</u>	1st Dosing	<u>4/14/81</u>	2nd Dosing	<u>4/15/81</u>	3rd Dosing
TIME DOSED:	<u>0800</u>		<u>2000</u>		<u>0800</u>	
DOSE (mg/kg):	<u>7.86</u>		<u>7.86</u>		<u>7.86</u>	
DRUG						

SIGNIFICANT ABNORMALITIES

DATE: 1981	2/25	4/13	4/14	4/15	4/16	4/17	4/20	4/27	5/4
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	21
1. Symptoms							X	X	
2. Physical Exam									
3. Urinalysis									
4. Biochemistry							X	X	
5. CBC		X		X		X	X	X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
SGPT	29	18	33	37	58H	112H	34	0-47 U/L
HCT	44.0	45.6	47.5	46.6	39.9L	44.3	45.2	40-50 Vol. %
Eosin	5	5	5	6H	6H	6H	6H	0-5 %
Retic.Count	N.D.	0.3L	0.4L	1.0	1.2	2.1H	1.5	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: When the subject returned for a follow up visit one week after dosing, he had poison ivy which progressed normally and was cleared by the end of the study. No other symptoms were exhibited. Physical exam was normal and remained unchanged except for the above mentioned poison ivy.

ABNORMALITIES COMMENT: SGPT elevated 58 Day 7, 112 Day 14, returned to normal Day 21. Other abnormalities minimal or inconsistent and not considered study related.

CONCLUSION: SGPT elevations possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 480 GROUP: H AGE: 24 WEIGHT: 80.45 kg HEIGHT 181.61

DOSING DATE:	1st Dosing <u>5/5/81</u>	2nd Dosing <u>5/5/81</u>	3rd Dosing <u>5/6/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>6.22</u>	<u>6.22</u>	<u>6.22</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/10	5/4	5/5	5/6	5/7	5/8	5/11	5/18	5/26
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	22
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry	X	X		X		X			X
5. CBC	X	X		X		X	X	X	

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
BUN	14	12	6L	11	13	10	13	9-21 mg/dl
Sodium	138	141	140	135L	141	139	140	137-151 mEq/L
T. Protein	5.9L	6.1L	5.8L	5.8L	6.5	6.4	6.5	6.4-8.0 g/dl
Albumin	4.1	4.1	3.9L	3.9L	4.2	4.2	4.0L	4.1-5.1 g/dl
Calcium	9.1	9.7	9.3	8.6L	9.7	9.1	9.1	9.0-10.9 mg/dl
Phosphate	3.0	4.1	3.9	4.8H	3.4	3.0	3.6	2.5-4.5 mg/dl
HgB	15.0	16.8H	15.8	15.8	15.9	16.2	15.9	13.3-16.7 GMS %
Lymphs	28	23	22	26	24	16L	23	19-59 %
Eosin	7H	7H	7H	7H	6H	5	5	0-5 %
UA - WBC	Neg	Occ	Neg	7H	Neg	Neg	Neg	0-5
Retic.Count	N.D.	1.0	1.8H	1.3	1.1	1.1	0.8	0.5-1.5 %
Monos	6	6	4	6	12H	5	8	0-10 %

KEY: H - high L - low ND - not done Neg - negative Occ - occasional

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. The physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 481 GROUP: H AGE: 24 WEIGHT: 59.09 kg HEIGHT 172.72

DOSING DATE:	1st Dosing <u>5/5/81</u>	2nd Dosing <u>5/5/81</u>	3rd Dosing <u>5/6/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>
PLACEBO			

SIGNIFICANT ABNORMALITIES

DATE: 1981	3/10	5/4	5/5	5/6	5/7	5/8	5/11	5/18	5/26
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	22
1. Symptoms									
2. Physical Exam									
3. Urinalysis									
4. Biochemistry		X							
5. CBC	X	X		X		X		X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Potassium	4.4	5.5H	3.8	4.7	4.1	3.9	3.8	3.6-5.2 mEq/L
HCT	51.4H	48.5	50.4H	47.0	44.1	48.4	50.5H	40-50 Vol. %
HgB	16.8H	16.8H	17.5H	16.3	15.2	16.8H	16.7	13.3-16.7 GMS %
MCH	31.1	33.2H	33.7H	33.9H	33.0	33.4H	32.2	27-33 G
Retic.Count	N.D.	1.1	1.2	0.4L	0.7	1.5	1.1	0.5-1.5 %
LDH	177	332H	173	129	138	138	164	72-233 U/L

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic throughout the study interval. The physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409-H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 482 GROUP: H AGE: 27 WEIGHT: 70.45 kg HEIGHT 178.44

DOSING DATE:	1st Dosing <u>5/5/81</u>	2nd Dosing <u>5/5/81</u>	3rd Dosing <u>5/6/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>0</u>	<u>0</u>	<u>0</u>

SIGNIFICANT ABNORMALITIES

DATE: 1981	4/14	5/4	5/5	5/6	5/7	5/8	5/11	5/18	5/26
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	22
1. Symptoms						X			
2. Physical Exam									
3. Urinalysis									
4. Biochemistry							X		
5. CBC					X				

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	93	77	83	103	65L	76	76	66-114 mg/dl
Retic.Count	N.D.	0.7	0.3L	0.6	1.1	0.5	1.0	0.5-1.5 %

KEY: H - high L - low ND - not done

SYMPTOMS AND PHYSICAL FINDINGS: The subject fainted after an unsuccessful venipuncture attempt 48 hours after third dosing. He was asymptomatic for the rest of the study. The physical exam was normal and remained unchanged throughout the study interval.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal and inconsistent and not considered study related.

CONCLUSION: No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 17: WR 180,409·H₃PO₄: SHORT TERM MULTIPLE DOSES:
SAFETY, TOLERANCE AND PHARMACOKINETICS.

CODE: 483 GROUP: H AGE: 22 WEIGHT: 71.36 kg HEIGHT 170.18

DOSING DATE:	<u>1st Dosing</u> <u>5/5/81</u>	<u>2nd Dosing</u> <u>5/5/81</u>	<u>3rd Dosing</u> <u>5/6/81</u>
TIME DOSED:	<u>0800</u>	<u>2000</u>	<u>0800</u>
DOSE (mg/kg):	<u>7.0</u>	<u>7.0</u>	<u>7.0</u>

DRUG

SIGNIFICANT ABNORMALITIES

DATE: 1981	4/14	5/4	5/5	5/6	5/7	5/8	5/11	5/18	5/26
STUDY DAY:	Screen	0*	1*	2*	3*	4*	7	14	22
1. Symptoms			X	X					
2. Physical Exam									
3. Urinalysis									
4. Biochemistry			X		X		X	X	X
5. CBC	X	X	X		X	X	X	X	X

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day	Scr	0	2	4	7	14	21	Normal Range
Glucose	75	82	77	83	68	65L	86	66-114 mg/dl
Creatinine	1.2	1.3	1.4	1.3	1.3	1.3	1.5H	0.8-1.4 mg/dl
Chloride	100	100	98	97L	102	99	100	98-110 mEq/L
Uric Acid	7.2	7.3	6.6	5.9	7.8	8.3H	7.9	4-8 mg/dl
T. Protein	7.5	7.8	8.2H	7.7	7.8	7.9	8.0	6.4-8.0 g/dl
Globulin	3.2	3.3	3.5H	3.3	3.3	3.4	3.5H	1.8-3.4 g/dl
Phosphate	3.5	3.7	4.0	4.9H	3.5	3.4	3.3	2.5-4.5 mg/dl
Cholesterol	238	227	265H	236	224	243H	220	110-242 mg/dl
Triglycerides	139	119	309H	155	105	129	127	0-207 mg/dl
RBC	5.61	5.49	5.91H	5.70	5.43	5.61	5.41	4.3-5.7 10 ⁶ /ml
Eosin	6H	7H	5	4	8H	7H	1	0-5 %
MCV	78L	80L	80L	79L	77L	79L	79L	82-98
MCH	26.4L	26.9L	27.5	27.2	26.6L	26.8L	26.2L	27-33 G
UA - WBC	Neg	4	3	7H	Neg	Neg	Neg	0-5
Retic.Count	N.D.	1.0	0.6	0.7	1.2	1.6H	1.1	0.5-1.5 %

KEY: H - high L - low ND - not done Neg - negative

SYMPTOMS AND PHYSICAL FINDINGS: Three hours after third dosing he complained of dizziness and nausea which was intermittent for about 24 hours. At that time after eating lunch he complained of feeling faint and passed out for few seconds. After lying down for a while he felt better but continued to complain of infrequent intermittent dizziness for 2 days. The physical exam was normal and remained unchanged throughout.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION: Dizziness and nausea possibly drug related.

NO STUDY ACTIVITY

SCHEDULED ACTIVITY ACCOMPLISHED

NS SUBJECT MISSED SCHEDULED ACTIVITY

(#) # = DAY ACTIVITY ACCOMPLISHED

= NUMBER OF SAMPLES TAKEN THAT DAY

EXPERIMENT #17: COMPLIANCE, GROUP A

	0	1	2	3	4	5	7	9	11	14	17	2
	3/2	3/3	3/4	3/5	3/6	3/7	3/9	3/11	3/13	3/16	3/19	3/1
Antoine Wilson	-	-	-	-	-	-	-	-	-	-	-	-
Physical	-	-	-	-	-	-	-	-	-	-	-	-
Interview	-	-	-	-	-	-	-	-	-	-	-	-
Vital signs	-	-	-	-	-	-	-	-	-	-	-	-
Lab tests	-	-	-	-	-	-	-	-	-	-	-	-
Dose 750 mg	-	-	-	-	-	-	-	-	-	-	-	-
Assay	-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-1	-

Robert Cole

453 Physical
Interview
Vital signs
Lab tests
Dose 750 mg
Assay

-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-3	-9	-2	-2	-2	NS ₂	-1	-1	-1	-1	-1	-

Leo Volz 454

Physical
Interview
Vital signs
Lab tests
Dose 750 mg
Assay

-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-1	-

Avon Stewart

455 Physical
Interview
Vital signs
Lab tests
Dose 750 mg
Assay

-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-	-
-	-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-1	-

EXPERIMENT #17: COMPLIANCE, GROUP B

	0 3/9	1 3/10	2 3/11	3 3/12	4 3/13	5 3/14	7 3/16	9 3/18	11 3/20	14 3/23	17 3/26	21 3/30
Thomas Trull	-											
Physical												/
Interview	/	/	/	/	/	/	/	/	/	/	/	/
Vital signs	/	/	/	/	/	/	/	/	/	/	/	/
Lab tests	/		/									/
Dose 750 mg		/	/									
Assay		/ 3	/ 9	/ 2	/ 2	/ 2	/ 1	/ 1	/ 1	/ 1	/ 1	/ 1

Donald Giancoli

457	Physical	/										/
	Interview	/	/	/	/	/	/	/	/	/	/	/
	Vital signs	/	/	/	/	/	/	/	/	/	/	/
	Lab tests	/										/
	Dose 750 mg		/	/								
	Assay		/ 3	/ 9	/ 2	/ 2	/ 2	/ 1	/ 1	/ 1	/ 1	/ 1

Stuart Varner

458	Physical	/										/
	Interview	/	/	/	/	/	/	/	/	/	/	/
	Vital signs	/	/	/	/	/	/	/	/	/	/	/
	Lab tests	/										/
	Dose 750 mg		/	/								
	Assay		/ 3	/ 9	/ 2	/ 2	/ 2	/ 1	/ 1	/ 1	/ 1	/ 1

Andre Blocker

459	Physical	/										/
	Interview	/	/	/	/	/	/	/	/	/	/	/
	Vital signs	/	/	/	/	/	/	/	/	/	/	/
	Lab tests	/										/
	Dose 750 mg		/	/								
	Assay		/ 3	/ 9	/ 2	/ 2	/ 2	NS 1/3/0	NS 1/0	/ 1	/ 1	/ 1

EXPERIMENT #17: COMPLIANCE, GROUP C

Dave Pinnick 460	0 3/16	1 3/17	2 3/18	3 3/19	4 3/20	5 3/21	7 3/23	9 3/25	11 3/27	14 3/30	17 4/12	21 4/6
Physical	✓			✓		✓						✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1000 mg			✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

Aaron Dorsey 461

Physical	✓			✓			✓					✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1000 mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

John Don Carlos

462 Physical

Physical	✓			✓			✓					✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1000 mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

Charles Spivey

463 Physical

Physical	✓			✓			✓					✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1000 mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

EXPERIMENT #17: COMPLIANCE, GROUP D

	0 3/23	1 3/24	2 3/25	3 3/26	4 3/27	5 3/28	7 3/30	9 4/1	11 4/3	14 4/6	17 4/9	21 4/11
Randolph Robinson												
Physical	✓			✓		✓						
Interview	✓	✓	✓	✓	✓	✓	NS			✓		
Vital signs	✓	✓	✓	✓	✓	✓	NS			✓		
Lab tests	✓		✓		✓		NS (8)			✓		
Dose 1000mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	NS 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

John Clarke 465

Physical	✓			✓								
Interview	✓	✓	✓	✓	✓	✓	✓					
Vital signs	✓	✓	✓	✓	✓	✓	✓			✓		
Lab tests	✓		✓		✓		✓			✓		
Dose 1000mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

Charles Sanders

Physical	✓		✓		✓							
Interview	✓	✓	✓	✓	✓	✓	✓					
Vital signs	✓	✓	✓	✓	✓	✓	✓					
Lab tests	✓		✓		✓		✓					
Dose 1000mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

David Johnson

Physical	✓		✓		✓							
Interview	✓	✓	✓	✓	✓	✓	✓			✓		
Vital signs	✓	✓	✓	✓	✓	✓	✓			✓		
Lab tests	✓		✓		✓		✓			✓		
Dose 1000mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

EXPERIMENT #17: COMPLIANCE, GROUP E

	0 3/30	1 3/31	2 4/1	3 4/2	4 4/3	5 4/4	7 4/6	9 4/8	11 4/10	14 4/13	17 4/16	21 4/20
Eric Nickel 468												
Physical	✓			✓		✓						✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1250mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

von Stewart 469

Physical	✓		✓			✓						✓
Interview	✓	✓	✓	✓	✓	✓	✓	NS		✓		✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	NS		✓		✓
Lab tests	✓		✓		✓			NS(e)		✓		✓
Dose 1250mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

Terry Hill 470

Physical	✓		✓			✓						✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1250mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

Steve Davis 471

Physical	✓		✓			✓						✓
Interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lab tests	✓		✓		✓		✓		✓	✓	✓	✓
Dose 1250mg		✓	✓									
Assay		✓ 3	✓ 9	✓ 2	✓ 2	✓ 2	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1	✓ 1

EXPERIMENT #17: COMPLIANCE, GROUP F

	0 4/6	1 4/7	2 4/8	3 4/9	4 4/10	5 4/11	7 4/13	9 4/15	11 4/17	14 4/20	17 4/23	21 4/24
Theodore Brown	/	/	/	/	/	/	/	/	/	/	/	/
472 Physical	/	/	/	/	/	/	/	/	/	/	/	/
Interview	/	/	/	/	/	/	/	/	/	/	/	/
Vital signs	/	/	/	/	/	/	/	/	/	/	/	/
Lab tests	/	/	/	/	/	/	/	/	/	/	/	/
Dose 1250 mg	/	/	/	/	/	/	/	/	/	/	/	/
Assay	/	/3	/9	/2	/2	/2	/1	/1	/1	/1	/1	/

Steve Raus 473

	/	/	/	/	/	/	/	/	/	/	/	/
Physical	/	/	/	/	/	/	/	/	/	/	/	/
Interview	/	/	/	/	/	/	/	/	/	/	/	/
Vital signs	/	/	/	/	/	/	/	/	/	/	/	/
Lab tests	/	/	/	/	/	/	/	/	/	/	/	/
Dose 1250 mg	/	/	/	/	/	/	/	/	/	/	/	/
Assay	/	/3	/9	/2	/2	/2	/1	/1	/1	/1	/1	/

Tom White 474

	/	/	/	/	/	/	/	/	/	/	/	/
Physical	/	/	/	/	/	/	/	/	/	/	/	/
Interview	/	/	/	/	/	/	/	/	/	/	/	/
Vital signs	/	/	/	/	/	/	/	/	/	/	/	/
Lab tests	/	/	/	/	/	/	/	/	/	/	/	/
Dose 1250 mg	/	/	/	/	/	/	/	/	/	/	/	/
Assay	/	/3	/9	/2	/2	/2	/1	/1	/1	/1	/1	/

Kwasi Baffour-Addae

	/	/	/	/	/	/	/	/	/	/	/	/
Physical	/	/	/	/	/	/	/	/	/	/	/	/
Interview	/	/	/	/	/	/	/	/	/	/	/	/
Vital signs	/	/	/	/	/	/	/	/	/	/	/	/
Lab tests	/	/	/	/	/	/	/	/	/	/	/	/
Dose 1250 mg	/	/	/	/	/	/	/	/	/	/	/	/
Assay	/	/3	/9	/2	/2	/2	/1	/1	/1	/1	/1	/

	0 4/13	1 4/14	2 4/15	3 4/16	4 4/17	5 4/18	7 4/20	9 4/22	11 4/24	14 4/27	17 4/30	21 5/4
Thomas Renner												
76 Physical	-		/		✓							✓
Interview	/	/	-	-	✓	✓	✓			✓		
Vital signs	-	-	-	-	✓	✓	✓			✓		
Lab tests	/		-		✓		✓			✓		
Dose 1500 mg			/									
Assay		/ 3	- 9	✓ 2	✓ 2	✓ 2	- 1	- 1	✓ 1	✓ 1	- 1	/ 1

John Chang 477

Physical	-		/			✓						-
Interview	-	-	-	-	✓	✓	✓			-		-
Vital signs	-	-	-	-	✓	✓	✓			-		-
Lab tests	-		-		✓		✓			-		-
Dose 1500 mg			/									
Assay		/ 3	- 9	✓ 2	✓ 2	✓ 2	- 1	- 1	✓ 1	- 1	- 1	- 1

Donald Giancoli

Physical	-		/			✓						-
Interview	-	-	-	-	✓	-	-			-		-
Vital signs	-	-	-	-	-	✓	-			-		-
Lab tests	-		/		-		-			-		-
Dose 1500mg			/									
Assay		/ 3	- 9	✓ 2	- 2	- 2	- 1	- 1	✓ 1	- 1	- 1	- 1

Scott Sherwood

Physical	-		/			✓						-
Interview	-	-	-	-	✓	✓	-			-		-
Vital signs	-	-	-	-	✓	-	✓			-		-
Lab tests	-		/		-		✓			-		-
Dose 1500mg			/									
Assay		/ 3	- 9	✓ 2	- 2	- 2	- 1	- 1	✓ 1	- 1	- 1	- 1

EXPERIMENT #17: COMPLIANCE, GROUP II

	0	1	2	3	4	5	7	9	11	14	17	21
Charles Spivey	5/4	5/5	5/6	5/7	5/8	5/9	5/11	5/13	5/15	5/18	5/21	5/22
480 Physical	-											-
Interview	-	-	-	-	-	-	-	-		-	-	-
Vital signs	-	-	-	-	-	-	-	-		-	-	-
Lab tests	✓									-	-	-
Dose 1500 mg		-	-									
Assay		-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-

Ivory Ross 481

Physical	-											-
Interview	-	-	-	-	-	-	-	-		-	-	-
Vital signs	-	-	-	-	-	-	-	-		-	-	-
Lab tests	-									-	-	-
Dose 1500 mg		-	-									
Assay		-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-

David Steinbacher

482 Physical	-											-
Interview	-	-	-	-	-	-	-	-		-	-	-
Vital signs	-	-	-	-	-	-	-	-		-	-	-
Lab tests	-									-	-	-
Dose 1500 mg		-	-									
Assay		-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-

Ivory Simon 483

Physical	-											-
Interview	-	-	-	-	-	-	-	-		-	-	-
Vital signs	-	-	-	-	-	-	-	-		-	-	-
Lab tests	-									-	-	-
Dose 1500 mg		-	-									
Assay		-3	-9	-2	-2	-2	-1	-1	-1	-1	-1	-

BIO - MED, Inc.

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EXPERIMENT NUMBER 18

TITLE:

WR 194,965-H₃PO₄: SHORT TERM
SAFETY AND TOLERANCE TO THREE
DIVIDED DOSES, RISING DOSE LEVELS.

PRINCIPAL INVESTIGATOR: JOHN A. JOHNSON, M.D.

CLINICAL DIRECTOR: KEVIN G. BARRY, M.D.

ASSOCIATE DIRECTOR: LESLIE B. ALTSTATT, M.D.

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BOARD MEMBERS:

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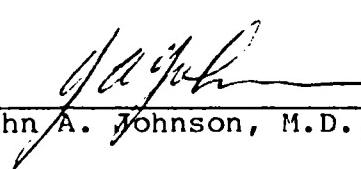
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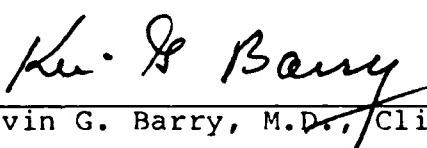
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INSTITUTIONAL CERTIFICATION

The professional staff of BIO-MED, Inc. has reviewed the protocol entitled: WR 194,965-H₃PO₄: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.

We recommend to the appropriate reviewing agencies and committees that the protocol be approved for implementation at BIO-MED, Inc.


John A. Johnson, M.D., Principal Investigator


Kevin G. Barry, M.D., Clinical Director


Leslie B. Altstatt, M.D., Assoc. Director

Concurrences:


Charles L. Pamplin, III, M.D.,
Major, MC
Contracting Officer Technical Representative (COTR)
DAMD 17-75-C-5036

TITLE: WR 194,965·H₃PO₄: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.

PURPOSE:

To establish the highest well-tolerated dose of WR 194,965·H₃PO₄ given in three divided doses at intervals of 12 hours.

RATIONALE OF STUDY:

WR 194,965·H₃PO₄ is an antimalarial of the Mannich base class.

In pre-clinical studies, the drug showed considerable promise as an antimalarial drug.

The drug has a CD₅₀ of 163 mg/kg (subcutaneously in peanut oil) in the mouse with rodent malaria and a CD₅₀ of 16.2 mg/kg (oral) in the Aotus monkey infected with the Smith Strain of falciparum malaria. Given orally to the Smith Strain infected Aotus at 35 mg/kg, it cured 100% of the animals studied in single doses or divided doses given over 3 or 5 days.

Animal toxicity studies show that the drug is well tolerated over the range of 8-35 mg/kg (oral). The curative dose for man has not been established. In a study of safety and tolerance with rising dose levels conducted at BIO-MED, Inc., single doses up to 1250 mg were given orally before intolerance was noted. At that dosing level, one of two subjects developed light-headedness, anorexia, nausea and self-induced emesis.

This drug is a promising candidate for studies of efficacy against induced malaria in man. However, safety and tolerance studies in man show that the top tolerated single oral dose is less than the dose that has cured 100% of Aotus monkeys infected with falciparum malaria. In this study, increasing doses of the drug will be given to subjects in three divided doses over a period of 24 hours, testing the assumption that higher total doses will be tolerated with divided doses than with single doses. A rising dose schedule will be followed with successive groups of subjects until intolerance* occurs or until the desired dose level is established.

* See "Monitoring" for discussion of intolerance.

METHODS:

Subject Acceptability Criteria

Subject acceptability criteria are based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects are rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest x-ray. The presence of conditions which do not increase risk for the subject or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes are not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean are cause for rejection. Deviations between 2 and 3 standard deviations from the mean are generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/dl would cause rejection, whereas a serum sodium of 153 mEq/L of itself would not. Subjects shall be between 60 and 90 kg in body weight, and within ten percent of ideal body weight.*

When doubt exists concerning acceptance of a subject for any reason, a decision is made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates are given full consideration and the integrity and ethics of the Research Team protected.

Subject Selection:

Approximately 32 male subjects between the ages of 18 and 35 will be recruited from the Washington, D.C. metropolitan area. No subject will participate more than once.

Candidates will be given a complete explanation of the background of the study, and of the procedures to be used in the study, and of all details of the protocol as it involves the individual subjects (see tab 1). They will be interviewed in a group and individually in the presence of an investigator. Each participant will be given the opportunity to ask questions. Following this, at the individual interview, the consent form (see tab 2) will be read and if the investigator believes the subject understands his participation adequately to give informed consent, the subject will be permitted to sign the consent form.

* Adapted from the Table of the Metropolitan Life Insurance Company. After Bray, G.A. Advances in Internal Medicine, Volume 21, page 270 Year Book Publishers 1976.

Following the consent process, candidates for employment will be medically evaluated to obtain the subjects for study. The medical evaluation will include a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential counts, red blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin.

Qualified candidates will be hired as temporary employees of BIO-MED, Inc.

Study Plan:

The study plan is summarized in the following schematic:

SCHEMATIC STUDY PLAN

Three Divided Doses of WR 194,965·H₃PO₄

Day of Study	0*	1*	2*	3*	4	14
Day of Week	M	T	W	TH	F	M
Physical Exam	X		X**		X	X
Interview	X	X	X	X	X	X
Vital Signs ⁺	X	X	X	X	X	X
Phototoxicity	X				X	
Lab Tests ⁺⁺	X		X		X	X
Dose			X---X			

* Controlled environment

** This examination to be done after 1400 hours.

+ Temperature, pulse, respiration, blood pressure, every 6 hours.

++glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

The design is a 2 X 2, double-blind, rising dose schedule with four subjects per level. The following table outlines the dosing schedule:

WR 194,965·H₃PO₄ DRUG ADMINISTRATION SCHEDULE

Group	1st dose	2nd dose	3rd dose	Total Dose
	Day 1 0800 hr	Day 1 2000 hr	Day 2 0800 hr	(mg)
A	500*	250	250	1000
B	500	500	250	1250
C	500	500	500	1500
D	750	500	500	1750
E	750	750	500	2000
F	750	750	750	2250
G	1000	750	750	2500

*Doses (in mg) of Drug or Placebo

There will be an interval of at least one week between dose levels.

On study day 1, the subject will reaffirm his consent in writing prior to his participation. The drug or the placebo will be ingested at the scheduled times in the presence of a staff nurse.

The drug will be supplied by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, in the form of 250 mg tablets labelled "WR 194,965·H₃PO₄". Unused drug and all containers will be returned to the Army Monitor.

SPECIAL PROCEDURES:

The standardized BIO-MED Phototoxicity Test (see tab 4) will be done on each subject on day 0 and day 3. Target sites will be examined 24 hours after exposure and re-examined until resolution if erythema develops. Codes revealing whether the subject received drug or placebo will not be broken until each respective subject has completed his participation in this study.

Monitoring:

Individual work sheets will be maintained on each subject. The following data will be recorded according to the schematic study plan: vital signs every 6 hours (including pulse, temperature, respiration, blood pressure, and weight), clinical and laboratory test results, symptoms and pertinent physical findings.

Signs or symptoms of possible drug intolerance will be carefully noted and thoroughly evaluated. Significant symptoms, physical findings, or laboratory deviations attributed to the drug shall be cause for suspension until BIO-MED and the COTR consult regarding continuation of the study. When ambiguity or uncertainty exists, the clinical director of BIO-MED, Inc. and the COTR may jointly decide to repeat any given dose level before proceeding to the next higher dose level.

On the last study day for each subject, final physical and laboratory evaluations will be done. All abnormal findings will cause follow-up until normalcy, stabilization or proper medical disposition is assured.

Emergencies:

The first priority will be to care for any subject in emergent need from any cause. Appropriate medical consultation will be obtained and hospitalization arranged where indicated. The COTR will be informed of any emergent incident in writing within 24 hours.

RESULTS AND REPORTING:

Individual summaries (see tab 3) will be prepared for each subject. All deviations from normal will be identified. Frequency distributions of inter-subject and intra-subject deviations will be prepared, providing a comparison of drug vs placebo effect at each dose level. BIO-MED, Inc. will prepare a final report when the study is completed.

BIO - MED, Inc.

EXPLANATION FOR POTENTIAL SUBJECTS

EXPERIMENT #18

WR 194,965·H₃PO₄: SHORT TERM SAFETY AND TOLERANCE TO THREE DIVIDED DOSES, RISING DOSE LEVELS.

Gentlemen:

The study for which you have applied involves taking by mouth the antimalarial drug WR 194,965·H₃PO₄. This is one of many antimalarial drugs being developed by the United States Army Medical Service, the sponsor of this study, in an effort to improve the treatment of drug resistant malaria. WR 194,965 has been approved for clinical testing in humans by both the sponsor and the Food and Drug Administration.

In a previous study of this drug conducted by BIO-MED, Inc., one subject who received a single dose of 1250 mg developed transitory nausea and self-induced vomiting. Several subjects experienced "light-headedness" which was not necessarily unpleasant and was not strictly related to the amount of drug. This symptom also occurred in a few subjects who received placebo (containing no active drug).

In this study a design called two by two, double-blind, rising dose schedule will be used. At each dose level, 4 subjects will be employed. Two will receive drug and 2 will receive placebo (no active drug). Neither the subjects nor the investigators know which subjects are receiving drug until the study for that dose level is completed. When that particular phase of the study is completed, codes will be broken and subjects will be told whether they received the drug or not. The amount of drug given is increased at each succeeding dose level. A new dose level is not started until the results of the seventh day of the previous dose level have been reported and evaluated.

In this study, the drug will be given by mouth in three doses at intervals of 12 hours, and the recipients will be closely monitored for well-being through vital signs (temperature, pulse, respirations, blood pressure), physical examinations and laboratory tests.

The plan of study is summarized in the following schematic:

SCHEMATIC STUDY PLAN

Three Divided Doses of WR 194,965·H₃PO₄

Day of Study	0*	1*	2*	3*	4	14
Day of Week	M	T	W	TH	F	M
Physical Exam	X		X		X	X
Interview	X	X	X	X	X	X
Vital Signs ⁺	X	X	X	X	X	X
Phototoxicity	X			X		
Lab Tests ⁺⁺	X		X		X	X
Dose				X---X		

* Controlled environment

+ Temperature, pulse, respiration, blood pressure every 6 hours.

++glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will done as clinically indicated.

WR 194,965·H₃PO₄ DRUG ADMINISTRATION SCHEDULE

Group	1st dose	2nd dose	3rd dose	Total Dose
	Day 1	Day 1	Day 2	(mg)
	0800 hr	2000 hr	0800 hr	
A	500*	250	250	1000
B	500	500	250	1250
C	500	500	500	1500
D	750	500	500	1750
E	750	750	500	2000
F	750	750	750	2250
G	1000	750	750	2500

*Doses (in mg) of Drug or Placebo

It is important that the blood be obtained at the times specified. It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol.

You must understand the risks to which you will be exposed in the course of this study. There are the risks, discomforts and inconveniences of residing in a clinical facility for a few days, and having routine measurements and venipunctures performed. Mild "sunburn" could develop at the site where your skin is exposed to a sun lamp in the phototoxicity test. In this study, there is a chance that you will develop nausea, vomiting, or abdominal discomfort. It is our expectation that if these symptoms develop, they will be minor and of short duration, and have no lasting effect upon your health. Finally, there is always the possibility of unexpected reactions to the drug. That possibility is minimal, but it should be taken into account.

You should know the policies and procedures followed at BIO-MED, Inc. to minimize the risk to your health and well-being. They are:

1. All procedures are conducted by a physician licensed in Maryland, or by a registered nurse or technician directly under the physician's supervision.
2. Each study to be conducted at BIO-MED, Inc. is reviewed by other agencies for compliance with Department of Health and Welfare Guidelines regarding volunteer participation in medical experiments. Those agencies are:
 - a. The Food and Drug Administration. This arm of the Federal Government reviews study proposals for investigational new drugs.
 - b. The Regulatory Agencies of the sponsoring bodies. In the case of studies sponsored by the U.S. Army, studies must be approved by the Human Use Committee of the Office of the Surgeon General of the U.S. Army.
 - c. The Institutional Review Board of BIO-MED, Inc. This board is made up of informed citizens from the local community. The board reviews each proposed study to see that the risks to the subjects are minimal, that precautions are taken to avoid risk when possible, and that risks are fully disclosed to the subject. The members of this board occasionally visit the clinical facility to inspect the conduct of a study.

3. To further insure your personal protection the following standard procedures are established:
 - a. Emergency medical treatment will be provided at nearby Doctors' Hospital of Prince George's County.
 - b. As a temporary employee of BIO-MED, Inc., you are protected by Workmen's Compensation for disability resulting by reason of your employment.
 - c. On your final day of participation, a complete physical examination and laboratory evaluation will be conducted. You will be informed of any abnormal findings, and should there be any, we will follow you until normalcy, stabilization or proper medical disposition is assured.

After members of the investigating team have interviewed you individually and are satisfied that you understand the study and the written informed consent form, you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent form, you signify that the study has been explained to you with regard to risks and requirements and that you wish to participate.

It should be clear to you that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to individuals who travel to these areas. Your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent and your participation at anytime without prejudice to yourself.

SUBJECT AGREEMENT
CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled "WR 194,965·H₃PO₄: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. _____, and are set forth in the document titled "EXPLANATION FOR POTENTIAL SUBJECTS, Experiment Number 18: WR 194,965·H₃PO₄: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.", which I have initialed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study. I also understand that my participation may be as a control subject.

I understand that as a temporary employee of BIO-MED, Inc. that Workmen's Compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at anytime; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

Date _____

Signature _____

Investigator Certification _____

Address _____

Witness _____

REAFFIRMATION OF CONSENT:

Date _____

Witness _____

Signature _____

BMI-300

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 18: WR 194,965-H₃PO₄: SHORT TERM SAFETY AND TOLERANCE TO:
THREE DIVIDED DOSES, RISING DOSE LEVELS.

TOTAL DOSE: _____ mg DOSING DATES: _____ CODE: _____
DOSE PER Kg: _____ mg/kg GROUP: _____ AGE: _____
HEIGHT: _____ cm WEIGHT: _____ kg

=====

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1981								
STUDY DAY:	Screen	0*	1*	2*	3*	4	14	
1. Symptoms								
2. Physical Exam								
3. Vital Signs								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								

KEY: X=abnormal (X)=abnormal, unchanged * =controlled environment

LABORATORY ABNORMALITIES SUMMARY:

ABNORMALITIES COMMENT:

CONCLUSION:

BIO - MED, Inc.

PHOTOTOXICITY PROCEDURE

PURPOSE: To determine immediate or delayed toxic response to U.V. Light.

EQUIPMENT:

1. Blak-Ray B-100A U.V. Lamp with spot bulb.
2. Blak-Ray J-221 Long Wave Ultraviolet Meter with reduction screen.
3. A 12-inch ruler.
4. A Marking Pen.
5. Dark or smoked glasses.
6. An accurate timer.

CALIBRATION:

Calibration will be done prior to studies requiring Photo-toxicity Testing. Target distance in inches will be done at 5, 5 1/2, 6, 7, 8, 9, and 10 inches.

To determine Joules:

$$\mu\text{W}/\text{cm}^2 = \text{B Scale Reading} \times 500 \text{ (To be recorded for each target distance).}$$

$$\text{Watts}/\text{cm}^2 = \mu\text{W}/\text{cm}^2 \times 10^{-6}$$

$$\text{Joules} = \text{Watts}/\text{cm}^2 \times \text{time in seconds}$$

Example:

$$\text{Target Distance} = 5 \text{ inches}$$

$$\text{B Scale Reading} = 60$$

$$\mu\text{W}/\text{cm}^2 = 60 \times 500$$

$$\mu\text{W}/\text{cm}^2 = 30,000$$

$$\text{Watts}/\text{cm}^2 = 30,000 \times 10^{-6}$$

$$\text{Watts}/\text{cm}^2 = 0.030000$$

$$\text{Joules} = 0.030000 \times 300 \text{ (5 minutes)}$$

$$\text{Joules} = 9.0$$

METHODS:

1. Place lamp horizontally on counter approximately 5 1/2 inches from counter lip. Allow 10 minutes lapse after activating lamp. Measure and record intensity in microwatts (μW).
2. Have subject sit with back exposed and touching counter lip. Using ruler adjust lamp distance to proper distance for correct joules from lamp rim to target spot on subject's skin. Circle target spot with marking pen and set timer for 5 minutes for white-skinned subjects and 10 minutes for dark-skinned subjects.

3. Check target stop frequently to be certain subject did not change position. Swing lamp away from subject when timer rings.
4. Use skin surface below tip of right scapula for target #1 and skin surface below tip of left scapula for target #2.
5. Calibration results will be included in study results.

TEST INTERPRETATION:

Targets will be read as specified in protocol, usually 24, 48 and 72 hours.

CAUTION:

Subject and operator must wear protective glasses. Lamp handle remains cool; however, lamp bulb may cause a burn if touched. Instruct subject and personnel accordingly.

DISTRIBUTION LIST

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